# 61. *Usnic Acid. Part VI. The Synthesis of* O-*Dimethylpyrousnic Acid.*

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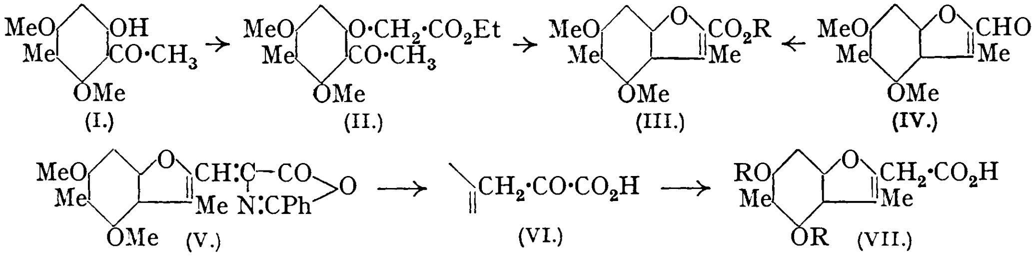
The observation that hydroxy- and methoxy-coumarones unsubstituted in the α-position yield α-formyl derivatives by the Gattermann reaction led to the preparation of 4 : 6-dimethoxy-2-formyl-3 : 5-dimethylcoumarone (IV), from which *O*-dimethylpyrousnic acid (VII) has been synthesised by the azlactone method, thereby confirming the constitution of pyrousnic acid, usnetic acid, and of decarbousnic acid. In order to test the method, the synthesis of 4 : 6-dimethoxy-3-methylcoumarone-2-acetic acid from the more accessible 4 : 6-dimethoxy-2-formyl-3-methylcoumarone was first studied. The orientation of the initial aldehydes has been conclusively established.

In Part IV (J., 1936, 1834) indirect synthetical evidence was adduced in support of the formula (VII, R = H) for pyrousnic acid (Part III, J., 1933, 1173; Asahina and Yanagita, *Ber.*, 1936, **69**, 1646), but since any formulation of usnic acid and of its main degradation products is primarily dependent on the structure of this compound (cf. Part V, J., 1937, 894, and Asahina and Yanagita, *loc. cit.*), it seemed highly desirable that the latter should be placed beyond doubt by a rational synthesis. This objective has now been achieved by the synthesis of *O*-dimethylpyrousnic acid according to a general method which depends on the observation that application of the Gattermann reaction to hydroxy- or methoxy-coumarones unsubstituted in the α-position leads to the formation of α-formyl derivatives (also unpublished work in this laboratory).

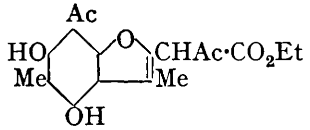
The *aldehyde* (IV) required for this synthesis was obtained in satisfactory yield from 4 : 6-dimethoxy-3 : 5-dimethylcoumarone and its orientation was established by the fact that on oxidation with potassium permanganate in aqueous acetone it gave rise to 4 : 6-*dimethoxy*-3 : 5-*dimethylcoumarone*-2-*carboxylic acid* (III, R = H), an authentic specimen of which was prepared from 2-*hydroxy*-4 : 6-*dimethoxy*-5-*methylacetophenone* (I) by way of the stages (II) and (III, R = Et). The ketone (I), which was obtained by isomerisation of the *acetate* of *C*-methylphloroglucinol β-dimethyl ether with aluminium chloride in nitrobenzene, could not be prepared by the condensation of *C*-methylphloroglucinol β-dimethyl ether and acetonitrile according to the method of Hoesch; in place of the expected ketimine a crystalline product was obtained which on hydrolysis regenerated the original phenol.

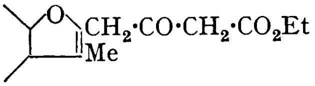


The pyruvic acid (VI) was formed by hydrolysis of the *azlactone* (V), obtained from the aldehyde (IV) in the usual manner, and on oxidation with alkaline hydrogen peroxide gave rise to the acid (VII, R = Me), identical in every way with a natural specimen of *O*-dimethylpyrousnic acid. In consequence, pyrousnic acid is represented by formula (VII, R = H) and hence the structures of usnetic acid and of decarbousnic acid (Part V, *loc. cit.*) are substantiated. In connection with the formation of the latter compound from usnic acid it may be noted that by a similar procedure Asahina and his collaborators (*Proc. Imp. Acad. Tokyo*, 1937, **33**, 270) have obtained an ester which, since it gave rise to acetic acid and usnetic acid or to carbon dioxide and deacetyldecarbousnic acid (Part V, *loc. cit.*) on alkaline fission, they consider to have formula (VIII).

Further, these authors claim that the formation of (VIII) supports the pyronone structure for usnic acid. It must be observed, however, that the ester in question may be equally well represented by formula (IX), which on hydrolysis would be expected to give the same

(VIII.)





(IX.)

products as (VIII), and consequently the objections to the pyronone structure for usnic acid outlined in Part V (*loc. cit.*) must be maintained at present.

On account of the fact that 4 : 6-*dimethoxy*-2-*formyl*-3-*methylcoumarone* is considerably more accessible than the aldehyde (IV) and in order to test the method, we studied, in the first instance, the synthesis of 4 : 6-dimethoxy-3-methylcoumarone-2-acetic acid. The orientation of the initial aldehyde was established by the procedure employed for the homologue (IV).

## EXPERIMENTAL.

4 : 6-*Dimethoxy*-3-*methylcoumarone*-2-*carboxylic Acid.*—This was prepared in satisfactory yield by the following modification of the procedure described by Kostanecki and Tambor (*Ber.*, 1909, **42**, 909), who obtained the compound in small yield. Interaction of 2-hydroxy-4 : 6-dimethoxyacetophenone (1·5 g.) and ethyl bromoacetate (1·6 g.) in boiling acetone (50 c.c.), containing potassium carbonate (1 g.), during 12 hours gave rise to ethyl 3 : 5-dimethoxy-2-acetylphenoxyacetate, which on isolation was warmed with alcoholic sodium ethoxide (from 0·09 g. of sodium and 5 c.c. of alcohol) on the steam-bath for 1 hour. Addition of water (75 c.c.) to the reaction mixture precipitated ethyl 4 : 6-dimethoxy-3-methylcoumarone-2-carboxylate, which separated from dilute alcohol in pale yellow needles (0·3 g.), m. p. 134°.

Acidification of the alkaline filtrate left on separation of the ester gave 4 : 6-dimethoxy-3-methylcoumarone-2-carboxylic acid, which formed colourless rods (0·9 g.), m. p. 242° (decomp.), from alcohol and was identical with the product obtained by hydrolysis of the ester with warm 10% aqueous-alcoholic sodium hydroxide for 1 hour (Found: C, 61·3; H, 5·2. Calc. for $C_{12}H_{12}O_5$: C, 61·0; H, 5·1%). On being warmed, the yellow solution of the acid in concentrated sulphuric acid became red and then deep red. With alcoholic ferric chloride the acid gave a red coloration, which appears to be due to the formation of a red ferric salt; the ester does not give a coloration.

3 : 5-*Dimethoxyphenoxyacetone.*—An ethereal solution of the product formed by the interaction of phloroglucinol dimethyl ether (15 g.) and chloroacetone (12 g.) in boiling acetone (225 c.c.), containing potassium carbonate (45 g.), during 3·5 hours was washed with 5% aqueous sodium hydroxide to remove unchanged phenol and then with water, dried, and evaporated. Distillation of the residue in a high vacuum gave the ketone as a pale yellow oil (10·3 g.), b. p. 127—132°/0·1 mm., the 2 : 4-*dinitrophenylhydrazone* of which separated from ethyl acetate in yellow needles, m. p. 152° (Found: C, 52·5; H, 4·6; N, 14·3. $C_{17}H_{18}O_7N_4$ requires C, 52·3; H, 4·6; N, 14·4%).

4 : 6-*Dimethoxy*-2-*formyl*-3-*methylcoumarone.*—Cyclisation of the foregoing ketone (1 g.) was effected with concentrated sulphuric acid (4 c.c.) at 0° during 5 minutes and the resulting 4 : 6-dimethoxy-3-methylcoumarone was precipitated with water (100 c.c.), isolated with ether, and purified by distillation in a vacuum, being obtained as a crystalline solid (0·3 g.), b. p. 100—102°/0·1 mm., m. p. 36°, identical in every respect with a specimen obtained by decarboxylation of 4 : 6-dimethoxy-3-methylcoumarone-2-carboxylic acid (Kostanecki and Tambor, *loc. cit.*).

A solution of the coumarone (1·8 g.) in ether (50 c.c.), containing hydrogen cyanide (0·4 c.c.), was saturated at 0° with hydrogen chloride and next day the dark green product was collected, well washed with ether to remove hydrogen chloride, and dissolved in water (50 c.c.). On being heated on the steam-bath for ½ hour, the green solution gradually became colourless and, on cooling, deposited the *aldehyde*, which formed colourless rods (0·9 g.), m. p. 155°, from alcohol (Found: C, 65·6; H, 5·5. $C_{12}H_{12}O_4$ requires C, 65·5; H, 5·5%). The 2 : 4-*dinitrophenylhydrazone* separated from much ethyl acetate in clusters of small red needles, m. p. 274° (Found: C, 54·1; H, 4·1; N, 13·7. $C_{18}H_{16}O_7N_4$ requires C, 54·0; H, 4·0; N, 14·0%).

Potassium permanganate (1·6 g.), dissolved in water (40 c.c.) at 45°, was gradually added to a solution of the aldehyde (1 g.) in acetone (25 c.c.) maintained at 50° and after having been kept at room temperature for 1 hour, the reaction mixture was cleared with sulphur dioxide. The resulting 4 : 6-dimethoxy-3-methylcoumarone-2-carboxylic acid was separated from a little unchanged aldehyde by means of aqueous sodium bicarbonate and then crystallised from alcohol, forming colourless needles (0·5 g.), m. p. 242° (decomp.), identical with an authentic specimen.

4 : 6-*Dimethoxy*-3-*methylcoumarone*-2-*pyruvic Acid*.—An intimate mixture of the aforementioned aldehyde (0·6 g.), hippuric acid (1 g.), sodium acetate (0·6 g.), and acetic anhydride (3·7 c.c.) was heated on the steam-bath for 1·5 hours, and the cooled reaction mixture treated with 50% alcohol (10 c.c.). Next day the *azlactone* was collected and recrystallised from acetic acid–alcohol, forming bright orange-red rods, m. p. 183·5° (Found: C, 69·3; H, 5·1; N, 3·7. $C_{21}H_{17}O_5N$ requires C, 69·4; H, 4·7; N, 3·9%).

This product (4 g.) was refluxed with 10% aqueous sodium hydroxide (60 c.c.) for 5 hours, and the cooled solution diluted with water (50 c.c.) and saturated with sulphur dioxide. Next day the benzoic acid was separated, and the liquor digested with concentrated hydrochloric acid on the steam-bath for 3 hours. The pyruvic acid, which separated from the acidic liquor as a pale yellow, micro-crystalline powder (2·5 g.), formed small prisms, m. p. 213—214° (decomp.), from dilute methyl alcohol and on oximation in alkaline solution gave rise to the *oxime*, which separated from water in clusters of colourless tiny prisms, m. p. 153° (decomp.) (Found: N, 4·8. $C_{14}H_{15}O_6N$ requires N, 4·7%).

4 : 6-*Dimethoxy*-3-*methylcoumarone*-2-*acetic Acid*.—30% Hydrogen peroxide (0·8 c.c.) was added dropwise to a solution of the foregoing pyruvic acid (0·5 g.) in 5% aqueous sodium hydroxide (10 c.c.), and 1 hour later the mixture was heated at 50° for 15 minutes, cooled, and saturated with sulphur dioxide. Crystallisation of the resulting precipitate from dilute alcohol gave the *acid* in colourless needles (0·4 g.), m. p. 148° (Found: C, 62·7; H, 5·7. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%). On being warmed, the yellow solution of the compound in sulphuric acid became deep red and then violet.

2-*Hydroxy*-4 : 6-*dimethoxy*-5-*methylacetophenone* (I).—Prepared by the pyridine–acetic anhydride method, the *acetate* of *C*-methylphloroglucinol β-dimethyl ether (Part IV, *loc. cit.*) separated from dilute alcohol in colourless prisms, m. p. 78·5° (Found: C, 62·9; H, 6·7. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%).

Aluminium chloride (1·64 g.) was added to a cooled solution of this acetate (2 g.) in nitrobenzene (8·2 g.) and 24 hours later the mixture was treated with ice-water, the product and nitrobenzene isolated by means of ether, the ethereal solution repeatedly extracted with 5% aqueous sodium hydroxide, and the combined extracts acidified with hydrochloric acid. On isolation with ether the product was dissolved in warm light petroleum (b. p. 60—80°) and, after cooling, the solution was filtered to remove a little *C*-methylphloroglucinol β-dimethyl ether and then evaporated. Distillation of the residue in a vacuum gave the *ketone* as a pale yellow oil (1·5 g.), b. p. 110—112°/0·2 mm., which gave a violet coloration with alcoholic ferric chloride (Found: C, 62·6; H, 6·7. $C_{11}H_{14}O_4$ requires C, 62·9; H, 6·7%). The 2 : 4-*dinitrophenylhydrazone* separated from benzene in brilliant red prisms, m. p. 205—206° (Found: C, 52·6; H, 4·9; N, 14·4. $C_{17}H_{18}O_7N_4$ requires C, 52·3; H, 4·6; N, 14·4%).

4 : 6-*Dimethoxy*-3 : 5-*dimethylcoumarone*-2-*carboxylic Acid* (III, R = H).—The product obtained by the interaction of the foregoing ketone (1·5 g.), ethyl bromoacetate (1·6 g.), and potassium carbonate (1 g.) in boiling acetone for 12 hours was warmed on the steam-bath with alcoholic sodium ethoxide (from 0·1 g. of sodium and 5 c.c. of alcohol) for 1 hour, and the resulting *ethyl* 4 : 6-*dimethoxy*-3 : 5-*dimethylcoumarone*-2-*carboxylate* (III, R = Et) precipitated with water (75 c.c.). Recrystallised from dilute alcohol, this ester formed almost colourless prisms having a negative ferric reaction (0·2 g.), m. p. 110° (Found: C, 64·6; H, 6·6. $C_{15}H_{18}O_5$ requires C, 64·7; H, 6·5%).

Acidification of the alkaline liquor left after separation of the ester furnished the *acid*, which formed colourless slender rods (0·8 g.), m. p. 219—220° (decomp.), from dilute alcohol and gave a red ferric reaction similar to that observed in the case of 4 : 6-dimethoxy-3-methylcoumarone-2-carboxylic acid (Found: C, 62·1; H, 5·8. $C_{13}H_{14}O_5$ requires C, 62·4; H, 5·6%).

4 : 6-*Dimethoxy*-2-*formyl*-3 : 5-*dimethylcoumarone* (IV).—The procedure employed for the preparation of 4 : 6-dimethoxy-3 : 5-dimethylcoumarone was similar to that described by Asahina and Yanagita (*Ber.*, 1937, **70**, 68); the intermediate 3 : 5-dimethoxy-4-methylphenoxyacetone gave a 2 : 4-*dinitrophenylhydrazone* which separated from ethyl acetate–alcohol in slender orange needles, m. p. 198° (Found: N, 14·1. $C_{18}H_{20}O_7N_4$ requires N, 13·9%).

On hydrolysis with water (75 c.c.) on the steam-bath for ½ hour the dark green aldimine which was obtained by the interaction of the coumarone (2 g.) with hydrogen cyanide (0·6 c.c.) in ether (75 c.c.), saturated with hydrogen chloride, gave rise to the *aldehyde*, which formed colourless prisms (1·2 g.), m. p. 127°, from alcohol (Found : C, 66·8; H, 6·0. $C_{13}H_{14}O_4$ requires C, 66·7; H, 6·0%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in tiny red prisms, m. p. 252° (Found : N, 13·7. $C_{19}H_{18}O_7N_4$ requires N, 13·5%).

Oxidation of this aldehyde by the procedure employed for the lower homologue gave rise to 4 : 6-dimethoxy-3 : 5-dimethylcoumarone-2-carboxylic acid, m. p. 219·5° (decomp.), identical in every way with an authentic specimen.

4 : 6-*Dimethoxy*-3 : 5-*dimethylcoumarone*-2-*pyruvic Acid* (VI).—Prepared by the interaction of the foregoing aldehyde (0·6 g.), hippuric acid (1 g.), sodium acetate (0·6 g.), and acetic anhydride (3·7 c.c.), the *azlactone* (V) formed slender orange rods (0·8 g.), m. p. 205°, from acetic acid–alcohol [Found : OMe, 16·2; N, 3·8. $C_{20}H_{13}O_3N(OMe)_2$ requires OMe, 16·4; N, 3·7%]. The *pyruvic acid*, obtained by the hydrolysis of the azlactone (2 g.) with boiling 10% aqueous sodium hydroxide for 6 hours, was isolated in the usual manner and separated from dilute acetic acid as a *hydrate* in pale yellow prisms, m. p. 190° (decomp.) [Found : C, 58·3; H, 5·5. $C_{15}H_{16}O_6,H_2O$ requires C, 58·1; H, 5·8%. Found for a specimen dried in a high vacuum at 80° : OMe, 21·0. $C_{13}H_{10}O_4(OMe)_2$ requires OMe, 21·2%].

4 : 6-*Dimethoxy*-3 : 5-*dimethylcoumarone*-2-*acetic Acid* (O-*Dimethylpyrousnic Acid*) (VII, R = Me).—This was obtained by oxidation of the foregoing acid (0·3 g.) with alkaline hydrogen peroxide. It formed colourless prisms (0·1 g.), m. p. 126°, from aqueous methyl alcohol, undepressed by admixture with a natural specimen (*loc. cit.*) [Found : C, 63·6; H, 5·9; OMe, 23·4. Calc. for $C_{12}H_{10}O_3(OMe)_2$ : C, 63·6; H, 6·1; OMe, 23·5%].

We are indebted to the Department of Scientific and Industrial Research for a maintenance grant to one of us (H. B.).

UNIVERSITY OF LIVERPOOL. [*Received, January* 19*th*, 1938.]